

research



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ORIGINAL RESEARCH Multicentre randomised trial

Comparative effectiveness of initial computed tomography and invasive coronary angiography in women and men with stable chest pain and suspected coronary artery disease

The DISCHARGE Trial Group

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Study question Do gender differences exist in the comparative effectiveness of computed tomography and invasive coronary angiography (ICA) in the management of patients with stable chest pain?

Methods This randomised multicentre pragmatic study of computed tomography versus ICA conducted at 26 centres in 16 European countries included patients with suspected coronary artery disease clinically referred for ICA for stable chest pain. The primary endpoint of this prespecified gender analysis was major adverse cardiovascular events (MACE: cardiovascular death, non-fatal myocardial infarction, or stroke). Key secondary endpoints were an expanded MACE composite (including transient ischaemic attack and major procedure related complication) and major procedure related complications.

Study answer and limitations Follow-up at a median of 3.5 years was available in 98.9% (1979/2002) of women and in 99.0% (1544/1559) of men. No statistically significant gender interaction was found for MACE, the expanded MACE composite, or major procedure related complications. For both genders, the

rate of MACE did not differ between the groups. In men, the expanded MACE composite endpoint occurred less frequently in the computed tomography group than in the ICA group (22 (2.8%) v 41 (5.3%); hazard ratio 0.52, 95% confidence interval 0.31 to 0.87). In women, the risk of having a major procedure related complication was lower in the computed tomography group than in the ICA group (3 (0.3%) v 21 (2.1%); hazard ratio 0.14, 0.04 to 0.46). The power of the gender comparison is limited by the sample size and small number of events.

What this study adds No evidence was found for a difference between women and men in the benefit of using computed tomography rather than ICA as the initial diagnostic test for the management of stable chest pain in patients with an intermediate pre-test probability of coronary artery disease.

Funding, competing interests, data sharing Funded by the comparative effectiveness research programme of the European Union (FP 2007-2013, EC-GA 603266). See bmj.com for competing interests. Requests for patient level data will be considered by the DISCHARGE Trial Group.

Trial registration [ClinicalTrials.gov](https://clinicaltrials.gov) NCT02400229.

Financial incentives for smoking abstinence in pregnancy

ORIGINAL RESEARCH Pragmatic, multicentre, single blinded, phase 3, randomised controlled trial

Effect of financial voucher incentives provided with UK stop smoking services on the cessation of smoking in pregnant women (CPIT III)

Tappin D, Sinclair I, Kee F, et al

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Study question Do financial incentives added to heterogeneous services to stop smoking in the UK help smokers to quit during pregnancy?

Methods Pregnant smokers were routinely identified at first maternity visit and referred to seven heterogeneous stop smoking services in the UK. The intervention was the offer of current service support with the addition of up to £400 (\$523; €583) of financial voucher incentives to engage with stop smoking services or to stop smoking during pregnancy compared with current service support, which includes the offer of counselling by specially trained workers using withdrawal orientated therapy and the offer of free nicotine replacement therapy. Self-reported abstinence of smoking for at least eight weeks during late pregnancy (34-38 weeks) was corroborated by saliva cotinine, a nicotine metabolite (and anabasine if using nicotine replacement products).

Study answer and limitations From 9 January 2018 to 4 April 2020, 941 (23% of 4032 screened; 471 intervention, 470 control) participants completed the study: three people asked for their data to be removed. 126 (27%) of 471 people in the intervention group and 58 (12%) of 470 in the control group stopped smoking (adjusted odds ratio 2.78 (95% confidence interval 1.94 to 3.97); $P < 0.001$). No evidence suggested that current services were disrupted. Most people who quit smoking from both groups relapsed after their baby was born.

What this study adds The offer of up to £400 of financial voucher incentives to stop smoking during pregnancy as an addition to current UK stop smoking services is effective.

Funding, competing interests, and data sharing Funded by Cancer Research UK, Chief Scientist Office Scottish Government, National Institute for Health Research Northern Ireland (NI), Public Health Agency NI, Chest Heart and Stroke NI, Scottish Cot Death Trust, and Lullaby Trust.

No competing interests declared. Data will be made available on reasonable request by York Trials Unit.

Study registration ISRCTN Registry ISRCTN 15236311.

Primary outcome derivation and primary analysis. Data are numerator/denominator (percentage) unless otherwise stated		
Outcome	Incentives	Control
Self-reported smoking status		
Non-smoker	169/472 (35.8)	87/472 (18.4)
Smoker	267/472 (56.6)	360/472 (76.3)
Missing self-report (assumed to be smoking)	36/472 (7.6)	25/472 (5.3)
No contact	25/36 (69.4)	16/25 (64.0)
Withdrew	11/36 (30.6)*	9/25 (36.0)*
Saliva test changed outcome from non-smoker to smoker		
Yes	19/169 (11.2)	13/87 (14.9)
No	126/169 (74.6)	58/87 (66.7)
Multiple appointments missed for saliva test (assumed to be smoking)	24/169 (14.2)	16/87 (18.4)
Biochemically verified smoking status (primary analysis)†		
Non-smoker	126/471 (26.8)	58/470 (12.3)
Smoker	345/471 (73.2)	412/470 (87.7)
*One intervention and two control participants withdrew and asked for their data to be removed.		
†Adjusted odds ratio 2.78 (95% confidence interval 1.94 to 3.97); $P < 0.001$.		

COMMENTARY A key opportunity to reduce health inequalities in early life

Tobacco smoking during pregnancy is associated with an increased risk of stillbirth, low birth weight, preterm birth, sudden infant death syndrome, asthma, and obesity among offspring.¹ Pregnancy is therefore an important window of opportunity to promote smoking cessation. Despite the risks, a substantial proportion of women worldwide still smoke during pregnancy.²

Behavioural support and nicotine replacement therapy can support attempts to stop smoking during pregnancy.^{3,4} Financial incentives can increase smoking cessation rates further,⁵⁻⁸ and the study by Tappin and colleagues adds evidence to support this.⁹ A major strength of this large trial is its pragmatic nature, with direct implications for implementation within the NHS.

Pregnant women from the trial's control group ($n=470$) received usual care, (behavioural support) provided by a stop smoking service, plus optional nicotine replacement therapy. The intervention group ($n=471$) received the same care and in addition were eligible to receive up to £400 (\$440; €455) in shopping vouchers to incentivise setting a quit date and remaining abstinent at four and 12 weeks follow-up, and in late pregnancy. The primary outcome was biochemically validated abstinence for at least eight weeks in late pregnancy. Secondary outcomes included continuous validated abstinence until six months post partum.

More women in the incentives group (335 (71%) of 469) than in the control group (301 (64%) of 470) engaged with the stop smoking services and set a quit date. Results showed an almost threefold increased odds in abstinence in late pregnancy in the

incentives group. Continuous abstinence rates at six months post partum were low in both groups (6% v 4%). Preliminary cost effectiveness analyses indicate that, over a lifetime, financial incentives were cost saving and improved health outcomes.¹⁰

Hard to reach

Probably the most important justification for offering pregnant women financial incentives to quit smoking is to protect unborn children. A financial incentive can support quitting by adding external motivation to existing internal motivation to stop smoking.¹¹

However, pregnant women who smoke can be a hard to reach group. In Tappin and colleagues' trial,⁹ 38% of women screened for eligibility could not be contacted and another 15% declined to participate, leaving an important part of the target group unserved. Among trial participants,

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Probably the most important justification for offering pregnant women financial incentives to quit smoking is to protect unborn children

more than two thirds were from the lowest two groups in the index of multiple deprivation. In another trial, from France, 40% of women were on low incomes.⁶

Offering financial incentives to pregnant women who smoke might be one of the few interventions that can reduce health inequalities in early life. Furthermore, smoking cessation interventions, including financial incentives for smoking cessation, are among the most cost effective interventions in healthcare, according to guidance from the US department for health and human services.¹²⁻¹⁴

Can Tappin and colleagues' findings be extrapolated to health systems outside the UK? Importantly, financial incentives for

smoking cessation are unlikely to be useful as a stand-alone intervention but need to be integrated into existing evidence based smoking cessation treatment programmes.¹¹

The UK has a fairly unique infrastructure in this respect. In Germany, for example, few specialised smoking cessation services are available, and the costs for behavioural support and pharmacotherapy for smoking cessation are generally not reimbursed by healthcare insurance.¹⁵ Of 14 trials evaluating financial incentives for smoking cessation in pregnant women,⁵⁻⁹ 11 were conducted in the US, two in the UK, and one in France. Given this current evidence base, generalisability of Tappin and colleagues' findings to countries with less well developed tobacco control policies and services is uncertain.

An important observation is that the partners of most pregnant women who smoke are also smokers (59% in Tappin and

colleagues' trial⁹ and >70% in the French trial,⁶ for example). This problem needs to be addressed, as a smoking partner is an important barrier to remaining abstinent from smoking during pregnancy, the risk of relapse after birth is increased, and environmental tobacco smoke in the house is harmful to children. Smoking cessation interventions should also be targeted at family members who smoke, to create a smoke-free home for mother and child.¹⁶

Furthermore, smoking cessation support for pregnant women should continue beyond childbirth to improve the disappointingly low long term abstinence rates. This support could include additional financial incentives during the postpartum period and might be specifically targeted at women on low incomes.

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Maternal hypertensive disorder of pregnancy and mortality in offspring from birth to young adulthood

Huang C, Wei K, Lee PMY, Qin G, Yu Y, Li J

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Study question Is maternal hypertensive disorder of pregnancy (HDP) associated with overall and cause specific mortality in offspring from birth to young adulthood?

Methods This cohort study examined the association of maternal HDP with overall and cause specific mortality in 2437 718 liveborn individuals from birth to young adulthood in Denmark, 1978-2018, with follow-up for four decades. Whether maternal diabetes and maternal education would have an additive effect on mortality in offspring, and whether the timing of onset and severity of HDP, specifically pre-eclampsia, has an influence were also investigated.

Study answer and limitations

102 095 mothers had HDP (67 683 with pre-eclampsia, 679 with eclampsia, 33 733 with hypertension). During follow-up, deaths occurred in 781 (58.94 per 100 000 person years) offspring exposed to pre-eclampsia, 17 (133.73 per 100 000 person years) exposed to eclampsia, 223 (44.38 per 100 000 person years) exposed to hypertension, and 19 119 (41.99 per 100 000 person years) not exposed to HDP. Maternal HDP was associated with a 26% (hazard ratio 1.26, 95% confidence interval 1.18 to 1.34) higher risk of all cause mortality in offspring. Increased risks were also observed for several cause specific mortalities, such as deaths from conditions originating in the perinatal period (2.04, 1.81 to 2.30), cardiovascular diseases (1.52, 1.08 to 2.13), digestive system diseases (2.09, 1.27 to 3.43), and endocrine, nutritional, and metabolic diseases (1.56, 1.08 to 2.27). Increased risks were more pronounced among offspring of mothers with early onset and severe pre-eclampsia (6.06, 5.35 to 6.86) or with both HDP and a history of diabetes (1.57, 1.16 to 2.14)



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or HDP and low education level (1.49, 1.34 to 1.66). Limitations of this study include possible residual confounding and misclassification of exposure, and generalisability, as Denmark has universal health coverage with high quality health services.

What this study adds Maternal HDP, particularly eclampsia and severe pre-eclampsia, is associated with increased risks of overall mortality and various cause specific mortalities in offspring from birth to young adulthood.

Funding, competing interests, and data sharing This study was funded by the National Natural Science Foundation of China, Shanghai Rising-Star Program, Shanghai Municipal Natural Science Foundation, Shanghai Municipal Science and Technology Major Project, the Independent Research Fund Denmark, the Nordic Cancer Union, the Karen Elise Jenssens Fond, and the Novo Nordisk Fonden.

No competing interests declared.
No additional data available.

Associations between maternal hypertensive disorder of pregnancy (HDP) and all cause mortality in offspring				
	No of deaths	Follow-up (person years)	Rate (per 100 000 person years)	Hazard ratio 95% CI
No maternal HDP	19 119	45 534 378.72	41.99	1.0 (reference)
Maternal HDP	1021	1 840 136.80	55.49	1.26 (1.18 to 1.34)
Pre-eclampsia or eclampsia	798	1 337 690.23	59.66	1.30 (1.21 to 1.40)
Severity of pre-eclampsia:				
Moderate	423	1 013 731.05	41.73	0.90 (0.82 to 0.99)
Severe	279	208 803.94	133.62	2.99 (2.66 to 3.37)
HELLP syndrome	30	18 671.24	160.67	4.79 (3.34 to 6.86)
Unspecified	49	83 772.24	58.49	1.30 (0.98 to 1.72)
Eclampsia	17	12 711.76	133.73	2.88 (1.79 to 4.63)
Hypertension	223	502 446.57	44.38	1.12 (0.98 to 1.28)
Pregestational hypertension	81	181 836.48	44.55	1.27 (1.02 to 1.58)
Gestational hypertension	142	320 610.09	44.29	1.06 (0.90 to 1.25)

HELLP=haemolysis, elevated liver enzymes, and low platelets.

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